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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/822,033	03/24/1997	WAYNE A. MARASCO	43471-FWC	5884

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EXAMINER	
WOITACH, JOSEPH T	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 10/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/822,033	MARASCO ET AL.	
	Examiner	Art Unit	
	Joseph T. Woitach	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *2/22/1994* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 4, 2005 has been entered.

DETAILED ACTION

This application is a file wrapper continuation of 08/199, 070, filed February 22, 1994.

Applicants' amendment filed August 4, 2005 has been received and entered. Claims 1, 3, 4, 13, 14, 15 have been amended. Claim 2 has been cancelled. Claim 17 has been added. Claims 1, 3-17 are pending and currently under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 5-7 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118 (a) states that "No amendment shall

introduce new matter into the disclosure of an application after the filing date of the application". Specifically, the claims have been amended to recite and encompass that a recombinant protein be made and that "the fusion protein has one amino terminus and one carboxyl terminus" (see claim 1) pointing to the specification in general and in particular figure 2. review of the present specification provides no literal support for the claimed embodiment. Review of figure 2 provides for a construct where two fusion proteins are made, and once expressed would result effectively in a light and heavy chain to form a complete recombinant antibody. In this case the fusion protein produced would have two amino and carboxyl termini in the protein formed. Figure 1, disclosing the use of a monoclonal antibody supports the use of sequences that result in multimeric proteins be used/formed.

To the extent that the claimed compositions and/or methods are not described in the instant disclosure, claims 1, 5-7 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as

filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure".

Claim Rejections - 35 USC 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-5, 7-16 stand rejected and newly added claim 17 is under 35 U.S.C. 103(a) as being unpatentable over Beug *et al.*, Chaudhary *et al.* and Wu *et al.* for the reasons below and as set forth in the previous office action.

Applicants' arguments are a duplicate of those provided in the after final amendment filed June 9, 2005. Applicants summarize the teachings of both Beug *et al.* and Wu *et al.* noting that each teach a fusion protein that is made by chemical conjugation of a targeting protein and

polycation, not a recombinantly made protein (middle of page 5). Applicants argue that while Chaudhary *et al.* teach a fusion protein, it is used to deliver a protein, not a nucleic acid as required by the instant claims. Further, there is no specific teaching nor motivation to use the teachings of Chaudhary *et al.* with that of Beug *et al.* and Wu *et al.*, therefore the use of fusion proteins for the targeted delivery of nucleic acids was not known at the time of filing (bottom of page 5, and 7-8). Giving the cited references, Applicants argue that Examiner's statement that the use of fusion proteins to delivery a polynucleotide is inaccurate (page 5). Noting the previously filed declaration of Dr. Wayne Marasco, a co-inventor and co-author on the Li *et al.* reference, Applicants argue that the use of recombinant fusion proteins provided surprising advantages over chemical conjugates (page 6). More specifically, Applicants argue that the data in the Li *et al.* reference provides clear evidence that the use of the ErbB2 antibody-protamine fusion protein provided a greater specificity than that of the chemical conjugate, pointing to figures 6C and 7B in the post-filing reference of Li *et al.* where an 8 to 10 fold increase higher expression in cells which express the ErbB2 cell surface receptor versus cells which do not express ErbB2 receptor is obtained using the fusion protein (page 6). Moreover, it is argued that one would expect that this approach would extend to other fusion proteins (top of page 7). See Applicants' amendment; pages 5-8. Applicants' arguments have been fully considered, but not found persuasive.

As indicated in the advisory action, Applicants argue that providing a recombinantly made fusion protein provides unexpected properties over one made chemically. Further, it is argued that post-filing art and the declaration of Dr. Marsco provide evidence supporting this assertion. Additionally, it is argued that while the cited reference teaches making a fusion

protein, this fusion protein was not used to deliver a nucleic acid. Applicants' arguments have been fully considered, but not found persuasive. As noted previously, Applicants arguments do not contest whether the cited references provide limitations that anticipate the embodiments of the claims nor the specific motivation for providing a recombinant fusion protein over a fusion protein made by chemical linkage. Applicants arguments focus primarily on the assertion that a recombinantly made protein would be more effective than one made chemically. Initially, it is noted that the present specfication does not provide any support for the fact that a recombinantly made protein would have any unique or unexpected property than one made recombinantly only that it could be assemble more readily or adapted more easily (see page 5 for example). With regard to evidence in Li et al and discussion in the declaration of Dr. Marsco regarding the evidence, Examiner would maintain that while one can compare qualitatively a quantitative comparison of the two compositions can not be done. As discussed previously, the differences between on how (or even why they were done) the experiments were conducted would not allow for a quantitative comparison. To make a informative quantitative comparison, the two compositions must be first somehow normalized to either binding capacity or even total protein used, then administered and compared directly. The difference in amount of fluorescence can not be attributed uniquely to the fusion protein and one has to take into the total of the two different experiments, for example amount/differences in the nucleic acid, the total amount of fusion protein used, the time at which expression was measured assaying fluorescence which in this case is affected by how long the luciferase assay was allowed to proceed when the measurement was finally made. At the time of filing, there is no dispute that fusion protein can be made (noting that Wu prefers the use of a peptide bond as a linker p. 8), that fusion proteins

were used to deliver polynucleotides, it is only contested that a recombinantly made fusion protein would be superior to one that was produced chemically. Given the evidence of record and in view of the breadth of the claims for a recombinant fusion protein made by any means (i.e. in cells that would not make an active or secreted form that would require re-folding for example). It is noted that Examiner would agree that a recombinantly made fusion protein used to deliver a polynucleotide was not specifically disclosed in the art at the time of filing (as presently claimed), however Examiner's statement that the use of fusion proteins is accurate because it was made in the context encompassing a fusion protein made by any means. More specifically, the teachings of Wu *et al.* provide evidence that a targeting molecule was fused, albeit chemically, to nucleotide binding agents such as polylysine, polyarginine, polyornithine, as well as other DNA binding protein known in the art such as hisotones, avidin, and protamines (page 7, bottom of the page). Here, Wu *et al.* clearly teach the combination of a cell targeting protein with a nucleotide binding molecule as one fusion protein. Because Wu *et al.* does not teach a chemical linkage that would result in the same fusion protein as one made recombinantly, the reference can not be used as anticipatory reference in a 102 type rejection. However, it does provide clear evidence that fusion proteins comprising the two protein elements recited in claim 1(a) were made and used to deliver polynucleotides (claim 1(b) limitation) at the time of filing. Thus, it is maintained that at the time of filing the use of fusion proteins for the delivery of polynucleotides was known.

Applicants do not contest that the cited references teach the limitations that anticipate the embodiments encompassed by the claims nor that there would be a reasonable expectation of success as required in making a *prima facie* case under 35 USC 103. The issue that remains is

whether the combined references provide adequate motivation to combine to make obvious the claimed product. As noted in the previous office actions, the instant specification teaches that the methodology used to generate a fusion protein is that known and conventional in the art at the time of filing. Again, the teachings in the present specification that a recombinantly produced protein is one which produced as one contiguous protein using conventional and standard molecular techniques known in the art (for example page 24, starting at third full paragraph). In the basis of the rejection Chaudhary *et al.* was cited to substantiate the statements in the instant specification regarding the technology of making recombinant fusion proteins. Further, Chaudhary *et al.* provides teaching for specific embodiments in the claims and a clear expectation of success for the use of recombinant technology in making fusion proteins. Examiner would agree that Chaudhary *et al.* does not teach nor provide the specific motivation to deliver a polynucleotide in the teachings, however as discussed above this is not why Chaudhary *et al.* is cited. The specific motivation to combine the teachings of the cited refrences comes from Beug *et al.* who teach fusion proteins for the delivery of polynucleotides, and that any method could be used to generate the fusion protein and specifically suggest recombinant technology. Similar to Wu *et al.* Beug *et al.* teach that when the peptides are coupled, for example a ligand to polylysine, and importantly that recombinant methods can be used to generate the recombinant protein (see for example page 7). Applicants= arguments that the combined references provide only for chemical linkage, is not persuasive because fusion proteins comprising two protein portions, one comprising a targeting moiety and one that binds a polynucleotide, were known in the art at the time of filing, and the cited references give specific suggestion to use methods known in the art such as generating them recombinantly.

Finally, regarding Applicants arguments that the declaration of Dr. Wayne Marasco, and evidence provided in the post-filing reference of Li *et al.*, demonstrates that the use of recombinant fusion proteins provided surprising advantages over chemical conjugates, in particular it is argued that the ErbB2 antibody-protamine fusion protein provided a greater specificity than that of the chemical conjugate, pointing to figures in the post-filing. In addition, it is argued that one would expect that this approach would extend to other fusion proteins. Upon examination of the experiments represented by the two figures referred to by Applicants, it is found that Applicants conclusion of surprising results can not be made. Initially, an analysis for the comparison of the two figures does not provide a comparison of recombinantly made and chemically linked fusion proteins. Figure 7 is simply a test of the affect on how the order of mixing the particular agents in the composition affect transfection. Moreover, a direct comparison can not be made because while the end point of luciferase activity was measured, the amounts of materials used and length of time before measuring luciferase activity are different. the experiments, each being critical in the final amount of gene delivered and expressed. In addition, a comparison of other fusion proteins indicates that the result relied upon in Applicants arguments is variable and dependent on the composition (compare for example ScFv-P-S and ScFv-P-L). Therefore, in light of the fact that figure 7 does not represent a chemically linked fusion protein and that the experiments of figure 6 and 7 were performed under different conditions, it is found that one can not draw any comparative conclusions that support an unexpected property of the claimed product over that in the prior art. It is noted that the present specification does not provide any evidence nor discussion for an unexpected property of the claimed invention. A complete reading of the Li *et al.* reference indicates that other

problems of recombinantly made fusion proteins also exist and was the reason for pursuing the compositions tested in figure 7(for example page 536). Even if one were to accept that a specific product had an unexpected property, based on the teachings of Li *et al.* as a whole for the problems of isolating the fusion protein and variability in different constructs, it is not apparent that the skilled artisan would agree with Applicants assertion that the approach would extend to other fusion proteins. Consistent with the rule that all evidence of nonobviousness must be considered when assessing patentability, the PTO must consider comparative data in the specification in determining whether the claimed invention provides unexpected results. *In re Margolis*, 785 F.2d 1029, 1031, 228 USPQ 940, 941-42 (Fed. Cir. 1986). However, " [i]t is well settled that unexpected results must be established by factual evidence. Mere argument or conclusory statements in the specification does not suffice." *In re De Blauwe* , 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984); see also *In re Wood* , 582 F.2d 638, 642, 199 USPQ 137, 140 (CCPA 1978) ("Mere lawyer's arguments and conclusory statements in the specification, unsupported by objective evidence, are insufficient to establish unexpected results."); *In re Lindner* , 457 F.2d 506, 508, 173 USPQ 356, 358 (CCPA 1972) (" [M]ere conclusory statements in the specification . . . are entitled to little weight when the Patent Office questions the efficacy of those statements.").

The claims broadly encompass any combination of targeting molecule and nucleic acid binding moiety. While the ScFv-P-S may display an 8-10 fold more luciferase activity to cells with than without ErbB2 (page 564 of Li *et al.*), clearly other constructs such as the ScFv-P-L which shows half the luciferase activity in ErbB2 expressing cells and greater non-specific activity (figure 6(c)) do not. In summary, at the time of filing Beug *et al.*, Chaudhary *et al.* and

Wu *et al.* provide the necessary teaching for all the embodiments encompassed by the instant claims, and the specific motivation to generate a recombinant targeting protein complex. In particular, where two protein components are provided, such as an antibody coupled to a second protein moiety, there is specific motivation to make this fusion protein recombinantly for the reasons set forth by Wu *et al.* and Chaudhary *et al.* Further, the use of a targeting antibody would generally be accepted to provide a more selective targeting, and as evidenced by Chaudhary *et al.* and Wu *et al.* the selection can be very great. Applicants arguments and reliance on unexpected properties of the claimed products are not found persuasive found nor convincing based on the evidence of record. Therefore, for the reasons above and of record, the rejection is maintained.

Claim 6 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Beug *et al.*, Chaudhary *et al.* and Wu *et al.* as applied to claims 1, 3-5, 7-16 above, and in further view of Ryder *et al.* for the reasons below and as set forth in the previous office action.

Applicants argue that the teaching of Ryder *et al.* does not overcome the essential deficiency of Beug *et al.*, Chaudhary *et al.* and Wu *et al.* as discussed for claims 1, 3-5, 7-16. See Applicants' amendment, page 8. Applicants' arguments have been fully considered, but not found persuasive.

As reasoned above, Beug *et al.*, Chaudhary *et al.* and Wu *et al.* provide the necessary teaching and motivation to make obvious claims 1, 3-5, 7-16. Beug *et al.* and Wu *et al.* teach that any variety of polynucleotide binding sequences can be used in forming the complexes and and attached to the targeting moiety, however specific polynucleotide sequences are not taught.

Ryder *et al.* is relied upon to teach that at the time of filing among the various species of sequences recited in claim 6, the Jun DNA binding sequences were known. As noted in the previous office action, Ryder *et al.* is not relied upon to correct deficiencies of Beug *et al.*, Chaudhary *et al.* and Wu *et al.*, rather the teachings are relied upon to teach what was known in the art at the time of filing. Ryder *et al.* provide a detailed teaching for the specific DNA binding sequences and demonstrate that they are effective in binding target DNA as evidenced by the gel shift assay (see results in figure). Applicants= arguments are unpersuasive because Beug *et al.*, Chaudhary *et al.* and Wu *et al.* provide the necessary teaching to make obvious claims 1, 3-5, 7-16, and claim 6 is obvious in light of the teaching of Ryder *et al.* for the specific c-jun DNA binding sequences.

Therefore, for the reasons above and of record, the rejection is maintained.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (571) 272-0739.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached at (571) 272-0735.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (571) 272-0532.

Joseph T. Woitach

1/20/06